Treatment Algorithms in Stage IV Melanoma

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Abstract: The molecular classification of melanoma and the advent of new drugs are changing the paradigm of therapy for advanced melanoma. A review of the recent key studies was performed, followed by a discussion in an expert forum. The aim of this review was to generate a therapeutic algorithm for stage IV melanoma. Tumor genotyping for BRAF and/or KIT should be performed before selection of therapy. For most BRAF-mutated melanoma patients and particularly those with a high tumor load, vemurafenib or other BRAF inhibitors such as dabrafenib are the treatment of choice. KIT inhibitors can be effective in KIT-mutant tumors, especially in those patients with mutations at exons 11 and 13. Ipilimumab is a good option for patients with nontargetable or nondetected mutations and those who progress under therapy with vemurafenib or a KIT inhibitor. There is still a role for conventional chemotherapy either as first-line treatment in BRAF wild-type patients or as salvage therapy in second or third line, or after other treatment modalities. Participation in clinical trials is strongly encouraged, either in first or in subsequent lines. New therapeutic options for advanced melanoma are guided by tumor genotyping. The current therapeutic algorithm includes kinase inhibitors, anti-CTLA4 therapy, immunotherapy, and chemotherapy, depending on the tumor genotype and response to previous treatments. Participation in clinical trials should always be encouraged because the treatment goal is long-term survival and potential cure in a subset of patients.

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Treatment Algorithms in Stage IV Melanoma

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The molecular classification of melanoma and the advent of new drugs are changing the paradigm of therapy for advanced melanoma. A review of the recent key studies was performed, followed by a discussion in an expert forum. The aim of this review was to generate a therapeutic algorithm for stage IV melanoma. Tumor genotyping for *BRAF* and/or *KIT* should be performed before selection of therapy. For most BRAF-mutated melanoma patients and particularly those with a high tumor load, vemurafenib or other BRAF inhibitors such as dabrafenib are the treatment of choice. KIT inhibitors can be effective in *KIT*-mutant tumors, especially in those patients with mutations at exons 11 and 13. Ipilimumab is a good option for patients with nontargetable or nondetected mutations and those who progress under therapy with vemurafenib or a KIT inhibitor. There is still a role for conventional chemotherapy either as first-line treatment in BRAF wild-type patients or as salvage therapy in second or third line, or after other treatment modalities. Participation in clinical trials is strongly encouraged, either in first or in subsequent lines. New therapeutic options for advanced melanoma are guided by tumor genotyping. The current therapeutic algorithm includes kinase inhibitors, anti-CTLA4 therapy, immunotherapy, and chemotherapy, depending on the tumor genotype and response to previous treatments. Participation in clinical trials should always be encouraged because the treatment goal is long-term survival and potential cure in a subset of patients.

Keywords: melanoma, advanced disease, BRAF inhibitor, MEK inhibitor, anti-CTLA4

INTRODUCTION

The management of metastatic melanoma has yielded disappointing results until recent times. Some patients obtained a benefit from regional treatments, but the majority of them required systemic therapy that was largely ineffective. Options included immunotherapy in selected centers (and for selected patients), clinical trials with new drugs, and, most commonly, chemotherapy.

Both new knowledge of the molecular biology of melanoma and the advent of ipilimumab and specific kinase inhibitors have dramatically changed this landscape. Melanoma is no longer envisioned as one single tumor but a constellation of diseases having specific molecular features. This new understanding allowed the development of BRAF inhibitors, for instance, and will likely foster the identification of other effective and specific drugs. As new compounds enter clinical

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trials and eventually become widely available, decision trees will be required to use them correctly.

This review summarizes evidence that may help in making clinical decisions and proposes an algorithm to use systemic treatments. A review of the recent key studies was performed, followed by a discussion in an expert forum. Local therapies will continue to play an important role in the management of regional disease but will not be covered in this review.

OPTIONS AND OUTCOME BEFORE THE ERA OF NEW DRUGS

The prognosis of patients with stage IV melanoma has remained unchanged for decades. A retrospective analysis published in 1983 showed a 1-year survival rate of 40% for stage IVA and 11% for stage IVC disease.[1] In 2000, the Eastern Cooperative Oncology Group reported a median overall survival of 8–10 months in patients with soft tissue or lung metastases and 6 months in those with visceral dissemination.[2] Numerous efforts to improve this outcome with the use of combined chemotherapy and immunotherapy proved to be unsuccessful. A systematic review of 41 randomized clinical trials revealed that combination regimens produced higher response rates, but at the cost of increased toxicity and with no benefit in overall survival.[3] These trials had used single-agent chemotherapy, combination chemotherapy, interleukin-2 with or without interferon or combinations of chemotherapy, and immunotherapy. In view of the limited success of complex schemes, single-agent therapy with dacarbazine, which achieves responses in 7%–15% of patients, was accepted as a reasonable standard of care in many institutions. Temozolomide and fotemustine were also used because they had similar activity and a favorable toxicity profile, and by crossing the blood–brain barrier, they have activity in brain-metastasized patients as well.[4–6]

Some types of immunotherapy stand out as exceptions to these poor results. Interleukin-2 yields complete remissions in 6% of patients, most of which are long-term survivors.[7] Because of the side effects in selected patients associated with this drug, it is usually restricted to young patients with excellent performance status and no comorbid conditions. Therapy with interleukin-2 is offered in selected centers with experience in the management of toxicity.

Adoptive cell therapy consists of the infusion of the patient's own tumor infiltrating lymphocytes after ex vivo expansion or antigen-specific T lymphocytes, that is, T-cell clones. The infusion is usually preceded by an immune-depleting regimen including chemotherapy or total-body irradiation. The procedure should be restricted to highly selected patients and requires a technology that is not widely available. In experienced hands, 3-year survival rates of up to 42% have been reported.[8,9]

ANTI-CTLA4 THERAPY

Ipilimumab is a fully humanized monoclonal antibody directed to CTLA4. Long-term survival in some patients was observed in phase 2 studies, although overall response rates were low.[10] A double-blinded phase 3 study in second line compared ipilimumab (3 mg/kg every 3 weeks) versus ipilimumab plus a gp100 vaccine versus the vaccine alone. Overall survival favored the ipilimumab arms, with 45.6% and 23.5% of the patients remaining alive at 1 and 2 years, respectively.[11] Another phase 3 study in first line compared dacarbazine versus dacarbazine plus ipilimumab (10 mg/kg every 3 weeks). Again, survival rates were superior in the ipilimumab arm: 47% versus 36%, 28% versus 18%, and 20% versus 12% at 1, 2, and 3 years, respectively.[12] Median overall survival was 11 months for the ipilimumab plus dacarbazine combination versus 9 months for dacarbazine alone. Although ipilimumab showed little benefit in overall response rate or progression-free survival, a survival plateau appeared after 2 years of follow-up, with 20% of the patients remaining alive in the long term. Based on these results, ipilimumab 3 mg/kg has been approved by the Food and Drug Administration (FDA) for first and second line, whereas the European Medicine Agency (EMA) and the Therapeutic Goods Administration in Australia approved it for second-line therapy. Interestingly, long-term benefit with ipilimumab does not seem to depend on the BRAF status.[13]

Ipilimumab was the first agent to demonstrate a significant overall survival benefit in metastatic melanoma but generated new issues. Standard criteria for the evaluation of response are not accurate for patients treated with ipilimumab, because initial lymphocyte infiltration in the tumor may increase tumor size or lead to the appearance of new lesions in computed tomography images (pseudoprogression). As a consequence, immune-related response criteria have been developed.[14] Furthermore, ipilimumab is associated with a new toxicity profile of immune-related side effects, mostly cutaneous and gastrointestinal, which requiring specific education and training of treating clinicians.

Future studies with the drug may be directed to the identification of predictive factors and the combination of ipilimumab with other drugs, such as BRAF inhibitors. Other agents that enhance the activity of the immune system are under development, such as those targeting PD1 and PD1 ligand. In the multicenter phase 1 trial, anti-PD1 ligand antibody was given

intravenously to a total of 207 patients as of February 2012. These included 55 with melanoma. Nine melanoma patients (of 52 who could be evaluated) showed an objective response, either complete or partial. Responses were durable in many patients, providing evidence that this line of therapy should be part of melanoma treatment in the future.[15,16]

SPECIFIC THERAPY IN BRAF-MUTATED MELANOMA

Approximately 40% of melanomas present mutations in *BRAF*, usually V600E and less commonly V600K and others.[17,18] This has allowed the development of specific kinase inhibitors. A diagram showing the role of BRAF in melanoma is given in Figure 1.[19]

BRAF inhibitors

Vemurafenib is a selective BRAF inhibitor that targets the V600 mutant forms of the *BRAF*.[20,21] Detection of the *BRAF* mutation can be done in paraffin-embedded specimens. The drug is active only in tumors harboring this kind of mutation, which needs to be detected before treatment initiation. Whenever possible, the mutation should be detected in metastatic tissue, as disparities have been reported between primary and metastatic lesions in some cases.[22]

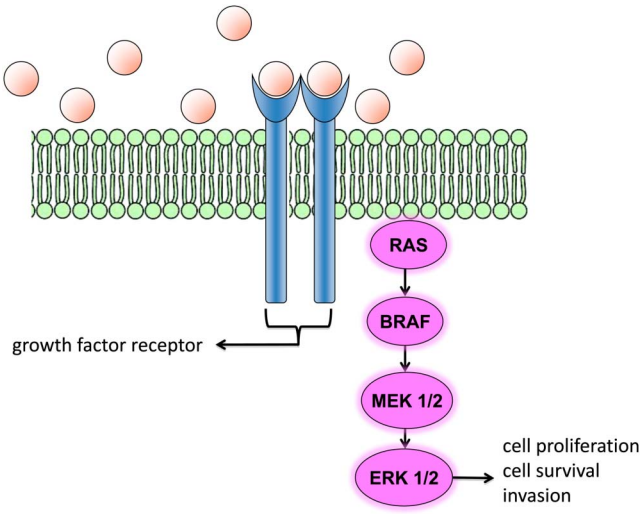

FIGURE 1. The BRAF-MEK pathway. Inappropriate activation of growth factor receptors (eg, KIT) or mutations of the *BRAF* gene can lead to constant activation of MEK 1 or 2, with resultant effects on cells: increased proliferation, survival, and propensity for invasion. The diagram is adapted from Meier et al.[19]

A phase 2 study of vemurafenib in second/third line showed objective responses in 53% of the patients and a median progression-free survival of 6.7 months.[23] The median overall survival was 15.9 months. The most common grade 3 adverse events requiring dose reduction were arthralgia, rash, UV A–dependent photosensitivity, fatigue, and elevated transaminases in 2%–5% of the patients.[23,24] Skin lesions such as squamous cell carcinoma and keratoacanthoma developed in 24% of the patients and were managed by surgical excision.

A subsequent phase 3 trial compared vemurafenib—960 mg every 12 hours—to dacarbazine in first line.[25] The first interim analysis showed a response rate of 48% for vemurafenib (vs. 5% for dacarbazine) and a median progression-free survival of 5 months (vs. 1.6). Based on these results, the FDA and the EMA have approved vemurafenib for the treatment of BRAF-mutated metastatic melanoma.

Vemurafenib is being investigated in a phase 1/2 study in combination with ipilimumab for advanced disease. There are also ongoing studies in patients with poor performance status or with brain metastases.[26–28]

Other BRAF inhibitors are being developed. Of these, dabrafenib (GSK118436) obtained results similar to those of vemurafenib in a phase 1/2 study.[29] A recent comparison of dabrafenib and dacarbazine in the BREAK-3 trial showed that dabrafenib demonstrated significant improvement in progression-free survival and overall relapse rate compared with dacarbazine.[30] Dabrafenib also showed significant activity in brain metastases with an overall response rate of 39% as first-line treatment and 31% in those who had previous brain radiotherapy.[31]

MEK inhibitors

MEK is a downstream target of the BRAF pathway, which is depicted in Figure 1. MEK mutation has been described as a possible mechanism of resistance to BRAF inhibitors.[32] Patients developing resistance to BRAF inhibitors frequently show reactivation of the MAPK pathway,[33] and a specific MEK inhibitor, trametinib (GSK1120212), has shown activity in patients who were progressing with a BRAF inhibitor.[34] A recent phase 3 study, the METRIC trial, compared trametinib versus chemotherapy with either dacarbazine or paclitaxel in patients with *BRAF*-mutant nonresectable melanomas. The results showed that trametinib conferred significant improvement in progression-free survival and overall survival compared with either chemotherapeutic modality.[35]

Combinations of specific inhibitors

Considerable effort is being dedicated to study the resistance to BRAF inhibitors and a number of mechanisms have been proposed. For instance, preclinical

models indicate the importance of MEK dependency in *BRAF*-mutant melanoma and suggest that a combination of BRAF and MEK inhibitors could prevent the emergence of resistance.[36] A phase 1/2 study of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib has shown encouraging activity with lower than expected toxicity. Among the 77 melanoma patients treated with this therapy combination, the overall response rate was 56% and the overall PFS was 7.4 months. The authors concluded that the combination had an acceptable safety profile along with antitumor efficacy.[37] Phase 3 trials comparing the MEK/BRAF inhibitor combination to BRAF inhibitor alone are currently underway.

Other mechanisms of resistance, independent of the BRAF or MEK pathways, have been described and point to new possible drug combinations.[38–42] At this time, the best strategy to prevent or overcome resistance to BRAF inhibitors remains unknown and will be the aim of future clinical trials. Given the heterogeneity of melanoma, it is unlikely that one particular combination will work in all cases.

KIT inhibitors

Approximately 15% of mucosal (with an especially high mutation rate in vulvovaginal melanomas[43]) and 23% of acral melanomas have a mutation or amplification in KIT,[44] which could allow therapy with specific inhibitors. A phase 2 trial of imatinib 800 mg/d in Chinese patients reported a partial response rate of 23% and stabilization in 30% of patients.[45] There is a clear hierarchy of mutations according to the response to targeted drugs with some mutations being completely resistant.[46] Most imatinib-sensitive mutations in melanoma are found in exons 11 and 13. In a phase 2 study from 28 patients with *KIT* mutation or amplification, 6 responded to the drug.[46] All of them had tumors with L576P or K642E mutations, the most common *KIT* mutations in melanoma. Experience in Western patients is more limited.[46] Likewise, the incidence of *KIT* mutation could differ depending on ethnicity. Ongoing studies (NCT01395121) have been launched for another specific inhibitor, nilotinib, in this population.

CONVENTIONAL CHEMOTHERAPY AND OTHER COMPOUNDS

Twenty percent of melanomas harbor mutations in N-RAS, whereas uveal melanomas typically have mutations in GNAQ or GNA11, and other melanomas yet show a variety of other mutations (PI3K pathway, MITF, CDKs, etc.).[47] MEK inhibitors, such as MEK162, could play a role in some of these less common subgroups of melanoma. This selective inhibitor of MEK1 and MEK2 showed clinical efficacy with good tolerability in an open-label phase 2 trial, among patients bearing BRAF- and NRAS-mutated melanoma.[47] Further basic research and multi-institutional cooperation will be critical in the future management of these subgroups.

However, chemotherapy has traditionally been associated with poor overall results, but some patients clearly benefit from this approach. For this reason, chemotherapy will still have a place as rescue strategy in second or third line and in patients with nonmutated melanoma.

A THERAPEUTIC ALGORITHM

As therapy for advanced melanoma becomes more complex, it is important to delineate treatment algorithms. Registration labels and drug availability will drive the sequence. At this time, ipilimumab and vemurafenib have been approved by regulatory agencies, although cost constraints may limit access in some countries. Other new drugs and combination options mentioned above remain experimental.

Considering the high response rate associated with vemurafenib, tumor genotyping is the first logical step in the algorithm (Figure 2). BRAF mutation should be searched for in all patients with metastatic melanoma.[48] An automated polymerase chain reaction–based diagnostic test has been developed and is approved by the FDA.[49] This test is very sensitive to detect V600E mutations but is less sensitive for non-V600E mutations. For this reason, if a mutation in *BRAF* is not found, ordering a second analysis by an alternative method could be justified. Acral and mucosal melanomas should also be tested for mutations in *BRAF* and *KIT*. NRAS mutational status should be determine in wilde-type BRAF melanoma, as MEK inhibitors are now under clinical evaluation in NRAS-mutated disease.[47]

Vemurafenib—and probably dabrafenib—is the preferred option in patients with *BRAF*-mutated melanoma. However, ipilimumab could be considered in low-risk patients, that is, those with low tumor burden and excellent performance status. Some of these patients could become long-term survivors, whereas the remaining would receive vemurafenib on progression with ipilimumab. As ipilimumab requires time to produce an effective response, patients with short life expectancy could be better served with other options.

Imatinib or another KIT inhibitor is indicated if a *KIT* mutation is detected, although evidence in this regard is less consistent than in the case of vemurafenib for

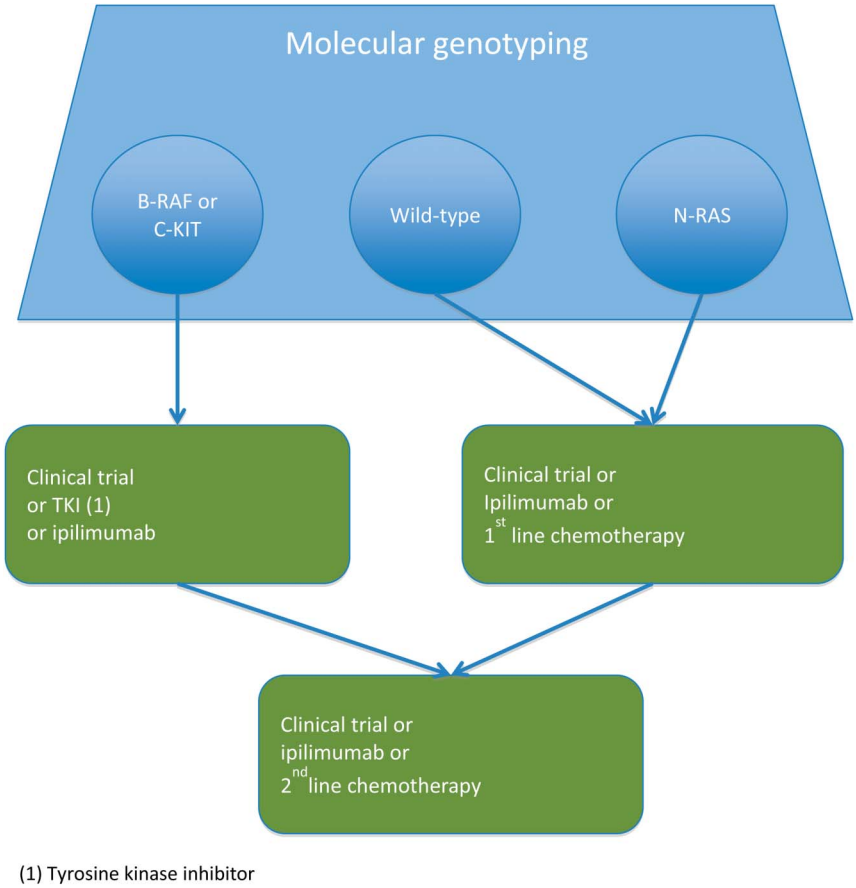

FIGURE 2. A therapeutic algorithm for advanced melanoma. Tumor molecular genotyping determines the options in first-line treatment. Kinase inhibitors are the therapy of choice if a specific mutation is detected, although data are more consistent for vemurafenib in *BRAF*-mutant melanoma than for KIT inhibitors in *KIT*-mutant tumors. Ipilimumab, chemotherapy, or immunotherapy can be considered in nonmutated melanoma as first line or in mutated melanoma after progression with specific drugs. It is very rarely possible to use ipilimumab after progression on BRAF inhibitors; the use of these drugs in the first line cannot be excluded.

BRAF-mutant melanoma. Ongoing studies will determine which *KIT* mutations are most amenable to treatment with this kind of inhibitors.

Patients progressing on vemurafenib or a KIT inhibitor could receive ipilimumab or chemotherapy, depending on performance status and drug availability. Ipilimumab should also be considered as first-line therapy whenever a targetable mutation is not detected in the tumor. Immunotherapy with interleukin-2 or adoptive cell therapy should be restricted to selected patients in centers with experience in these treatment modalities.

The importance of clinical trials cannot be overemphasized. The possibility to refer patients for clinical investigation should be considered at any stage of the patient's evolution. The algorithm will be subjected to changes as new alternatives demonstrate efficacy for specific subgroups. For instance, MEK inhibitors or the combination of BRAF and MEK inhibitors might be considered in first-line for *BRAF*-mutated melanomas. In the future, specific drugs could be developed to treat melanoma with other mutations, in which the detection of these mutations should become the standard of practice. Likewise, if markers predicting response to ipilimumab or anti-PD1 antibodies are finally found, they should be incorporated to the pathological workup.[16]

CONCLUSIONS

In 2012, therapy for advanced melanoma is determined by the mutational status of the tumor. Vemurafenib is the most active agent in *BRAF*-mutant melanoma, whereas a KIT inhibitor could be considered in tumors with a mutation in *KIT*. Ipilimumab should be

considered as first-line for patients with no target mutations or as second line in any patient. Chemotherapy may have a role as salvage therapy in second or third line.

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